solubility. The invention is based, *inter alia*, on the finding that there are differences in equilibrium solubility among the salts of a given drug in a specific cyclodextrin. That is, Applicant made the determination that different salts of a given compound can have different solubilities in the same cyclodextrin. The art previously believed that a salt of a drug dissolves in a cyclodextrin-containing aqueous media by simply dissociating to form a charged drug molecule and a counter-ion, and that the dissociated (i.e., charged) drug molecule is the guest moiety which forms the inclusion complex with the cyclodextrin. A consequence of this belief was the corollary belief that there are no differences in equilibrium solubility among the salts of a given drug in a specific cyclodextrin. This is explained in Applicant's specification on page 2, lines 14-27. As a consequence of the foregoing beliefs, the art nowhere discloses locating a salt having a solubility greater than a threshold solubility (i.e. greater than a desired target solubility), by Applicant's method or anything approaching it.

The rejection under 35 USC 112

Claims 1 and 2 stand rejected under 35 USC 112, second paragraph, as being indefinite. In the Office Action of February 7, 2000, the Examiner stated, in pertinent part, in paragraph 6, page 2:

> "Applicant argues against this rejection on the grounds that the term "desired target solubility" was completely clear and distinct without the abundant explanation given in Applicant's specification, but that, especially in light of the explanation (and exemplification) of "desired solubility" supplied by Applicant in the specification, one skilled in the art, would find the claims to be clear and distinct, and have no difficulty understanding the metes and bounds of the subject matter claimed. However, this argument is not persuasive since the metes and bounds of the term "desired target solubility" cannot be determined without further explanation in the claims as to the exact solubility that is desired by the Applicant. Furthermore, this terminology does not fulfill the requirement of 35 U.S.C. 112, second paragraph, since this language does not point out and distinctly claim the subject matter and the specification does not provide a standard for ascertaining the requisite degree of the term. [Page 2, paragraph 6 of the Official Action].

The rejection is traversed on the basis that one skilled in the art, particularly in view of the explanation and definition given in the specification, would readily understand the meaning of the term "desired target solubility", and thus be able to determine the metes and bounds of the claims. It is noted that this is all that the second paragraph of § 112 requires - - that the claims set out and circumscribe a particular area that the applicant regards as the invention with a reasonable degree

of precision and particularity. See In re Borkowski, 164 USPQ 2d 642 where it was stated

> The first sentence of the second paragraph of §112 is essentially a requirement for *precision* and *definiteness* of claim language. If the scope of subject matter embraced by a claim is clear, and if the applicant has not otherwise indicated that he intends that claim to be of a different scope, then the claim does particularly point out and distinctly claim the subject matter which the applicant regards as his invention. [164 USPQ at 645-46; emphasis in original]

The Examiner, as quoted above, has taken the position that the term "desired target solubility" does not point out and distinctly claim the invention because (1) the term cannot be determined without further explanation in the claims as to the exact solubility that is desired by the Applicant. and (2) the specification does not provide a standard for ascertaining the requisite degree of the term.

Applicant takes the position that (1) an Applicant is allowed to be his own lexicographer; (2) definiteness of claim language must be analyzed not in a vacuum, but in light of the specification and the prior art; *In re Marosi*, 218 USPQ 289 (Fed Cir 1983); (3) it is the function of the specification to explain the meaning of terms, not the claims; and (4) Applicant has gone out of her way in her specification to explain and exemplify exactly what is intended by the phrase at issue. See page 4, line 25 to page 5, line 14 of the application where it is stated:

> A "desired target solubility" as used herein can be a mimimum solubility, usually pre-determined or pre-chosen, required for the compound being tested. The required minimum solubility will generally be chosen on the basis of therapeutic need. For example, assume that it is desired to administer 20 mg of a compound ("Compound X") parenterally, by injection, and that it is desired to administer an injection volume of not more than 2 ml to minimize pain on injection. Thus a salt of Compound X, in order to be "useful", would need to have a solubility, in the chosen aqueous cyclodextrin, equivalent to or greater than 10 mg/ml of Compound X in its active form.
>
> Within a given series of salts, the most soluble salt may not be the most useful candidate for a given application. Factors such as chemical stability, hygroscopicity, and the potential for precipitation may also be considered and weigh in favor of choosing a candidate having a solubility greater than the target solubility, but less than the maximum determined within the series.
>
> On the other hand, at times it may indeed be desired simply to find the salt with the highest solubility of all salts within a series of salts of a particular compound. In this case the "desired target solubility" is simply the highest solubility encountered in the series of salts by comparison of equilibrium solubilities among the various salt candidates. For example, if it is desired to make a dry oral dosage form such as a capsule or tablet using an inclusion complex of a salt of Compound X, then it may be desired simply to find the most soluble

> salt available in order to minimize the amount of inclusion complex in the dosage form, and thereby minimize the size of the dosage form itself.

Surely the Examiner will agree that the above quoted explanation for the objected-to-phrase is sufficient to explain to anyone skilled in the art just exactly what is intended. Applicant has defined the term extensively and even explained how and why one would go about determining a desired target solubility. The above quotation illustrates that Applicant has gone to great lengths to make sure that the phrase "desired target solubility" is fully understood within the context of the instant invention. The first paragraph notes that a desired target solubility will generally be some pre-determined or pre-chosen solubility selected on the basis of therapeutic need, and gives a hypothetical numerical example to illustrate exactly what is intended. The next paragraph explains that the salt having the maximum solubility determined within a series of salts may not always be selected simply because it is the maximum. Other factors, for example chemical stability, hygroscopicity, and the potential for precipitation, are mentioned which may weigh in favor of choosing a candidate having a solubility greater than the target solubility, but less than the maximum solubility determined within a series of salts. The skilled art worker reading Applicant's disclosure would immediately realize that a "desired target solubility" is a threshold solubility needed to effect therapeutic efficacy in a dosage form, the threshold being the desired target solubility. The skilled worker would also realize that the actual salt selected need not be the most soluble salt found so long as its solubility meets or exceeds the target solubility.

Applicant further included a detailed example, Example 3, which goes into great detail as to how salts having a desired target solubility would be chosen for adult and pediatric patient subsets when, because of differing therapeutic requirements for each different patient subset, the desired target solubility differs as well with respect to each subset. The example discloses a series of salts and explains exactly how desired target solubilities, and salts satisfying such targets, would be chosen. The example thus adds understanding to the already well-explained term at issue.

Further, explanation is not required to be placed in the claims, as implicitly contended by the Examiner iin the Febryuary 7, 2000 Office Action. Enablement and description, including explanation, are the functions of the specification. As stated above, Applicant has gone to great lengths to ensure that the phrase "desired target solubility" would be well understood by an interested reader. The claim is otherwise

clear and distinct and those skilled in the art would have no difficulty understanding the subject matter intended. That is all that the second paragraph of §112 requires. The Patent Act "requires only reasonable precision in delineating the bounds of the claimed invention." United States v. Teletronics, Inc., 8 USPQ2d 1217 (fed. Cir. 1988). Also,

> The test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification... If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, §112 demands no more.

See Miles Laboratories Inc. v. Shannon Inc., 27 USPQ2d 1123 (Fed. Cir. 1993), at page 1126.

For all of the above reasons, it is respectfully submitted that the rejection under Section 103 is simply not tenable for this application, which was originally drafted to ensure that the disputed term "desired target solubility" would in fact be well understood. In view of the above comments, it is requested that the rejection under 35 USC §112 be withdrawn.

The Section 103 Rejection

Claims 1-3 continue to be rejected under 35 USC 103(a) as being unpatentable over Bryant, US 5,624,940, Applicant's previous arguments having been deemed not persuasive. The Examiner stated, in pertinent part:

> ...Applicants argument on pages 3 and 4 of their response filed November 29, 1999 is not persuasive since the metes and bounds of Applicants desired target solubility cannot be determined. The claims do not specific any particular salt of a compound and only indicated that the salts of the compound are being made soluble by combining the salts of the compound with cyclodextrin, which is well known in the art as indicated in the Bryant et al patent. The fact that Applicants are determining the solubility of a series of salts (which have not been specifically set forth in the claims) does not make the claims patentable over the prior art. Accordingly, the rejection of the claims under 35 U.S.C. 103(a) as being unpatentable over the Bryant et al patent is maintained.

In discussing Applicant's traversal, it would be useful and convenient to reproduce claim 1:

> 1. A method of locating one or more salts of a compound, said salts having a solubility in a cyclodextrin equal to or greater than a desired target solubility, comprising obtaining a series of salts of said compound, determining the equilibrium solubility of each salt in said series in an aqueous solution of said cyclodextrin, and comparing each measured solubility with said target solubility.

Bryant does not disclose "obtaining a series of salts of said compound", as required by Claim 1. Nor does Bryant disclose "determining the equilibrium solubility of each salt in said series in an aqueous solution of said cyclodextrin", as also required by Claim 1. Nor does Bryant disclose "comparing each measured solubility with said target solubility" as also required by Claim 1. None of these elements is disclosed or suggested by Bryant, and the Examiner has provided no basis for arguing or concluding otherwise. The same or similar arguments can be made for claims 2 and 3. Because Bryant does not disclose or suggest these claim elements, it is simply not seen how Applicant's invention can be obvious, and the rejection is traversed on that basis.

The rejection is further traversed on the basis that Bryant does not disclose that different salts of the same compound have different solubilities in the same cyclodextrin, and, for that matter, teaches nothing relating to determining any solubility above any minimum or threshold level, i.e., Bryant discloses nothing relating to determining a desired target solubility.

So far as the Examiner's comments in paragraph 8 of the February 7, 2000 Office Action which relate to "the metes and bounds of Applicant's desired target solubility cannot be determined" are concerned, Applicant's comments above relating to this issue are incorporated by reference. Applicant's method is intended to be general so that it can be used to find a useful salt (i.e., one having a solubility equal to or greater than a desired target solubility) for any compound. The method is not limited to any particular salts or to any particular compounds. Because of the method's generality, it would totally defeat the purpose of the invention to specify particular salts in the claims, and thereby limit the claims, as suggested by the Examiner. It would be equally self-defeating to specify a particular "series of salts" in the claims, as also implicitly suggested by the Examiner. That would again needlessly limit the claims to that particular series of salts even though the invention does not reside in any particular series of salts. The point is that It would not be obvious to test a series of salts to see which one exceeds a pre-determined or desired (i.e., target) solubility if conventional wisdom was that the salts would all have the same solubility in the first place.

Bryant does nothing to bridge the gap between the prior art and Applicant's invention. Bryant simply teaches a series of compounds, notes that the compounds can form the usual pharmaceutically acceptable acid addition and base addition salts, and discloses that cyclodextrin inclusion complexes can be made. Bryant discloses nothing about any one salt of a compound having a greater solubility in a

given cyclodextrin than any other. Bryant discloses nothing about any method for making such a solubility determination within a series of salts, and fails to even remotely mention the feasibility for doing so. There is emphatically no disclosure, teaching or recognition in Bryant that any salt of a given compound would be any more or less soluble in a given cyclodextrin than any other salt in the same cyclodextrin. There is not even the slightest indication that different salts of the same compound can have different solubilities in a given cyclodextrin, i.e., of the very finding that, *inter alia*, underlies Applicant's invention.

It is noted that in the Advisory Office Action dated May 30, 2000, the Examiner made the following (handwritten) statement:

> Bryant is drawn to the selection of useful salt inclusion complexes of cyclodextrin, and therefore meets the claims. While Bryant et al does not de-select any salts, neither does the process of the present invention.

With respect to Applicant's claims 2 and 3, the above statement is simply wrong in the conclusion that "...neither does the process of the present invention". Both claims specifically require a "selecting" step, see step (c) in claim 2 and step (f) in claim 3. The process of selecting, in turn, implies that a "de-selection" of other salts may need to be made, i.e., if such other salts do not have a solubility equal to or greater than a desired target solubility.

Claim 1 does not employ the word "select", as do claims 2 and 3. That is immaterial, however, since Bryant fails to disclose any of the other steps required by claim 1 - - obtaining a series of salts, determining the equilibrium solubility of each salt in the series in an aqueous solution of a given cyclodextrin, and comparing the equilibrium solubility of the measured solubility with a target solubility.

The Examiner is also in error in stating that "Bryant is drawn to the selection of useful salt inclusion complexes of cyclodextrin..." Bryant simply discloses that cyclodextrin complexes of different salts of his formula (I) compounds can be made. Bryant never discloses "selecting" anything, including "selecting" any cyclodextrin complex relative to any other. Simply disclosing salts and disclosing cyclodextrins which can be used to complex the salts is not the same as "selecting", and the Examiner has not provided any basis otherwise.

Thus, Bryant, read in context, (1) never suggests that any particular salt of a compound of his formula (I) is any more soluble in a given cyclodextrin than any other salt made with any other acid or base also disclosed therein, (2) never touches on how such a salt would be located, and (3) never even remotely suggests the

possibility or feasibility of doing so. Bryant neither discloses, suggests, nor motivates anything relating to Applicant's method, and could not without a recognition of Applicant's finding, discussed above, that different salts of a given compound have different solubilities in the same cyclodextrin. Again, the Examiner has provided no basis otherwise. Without such suggestion or motivation it is simply not possible for Bryant to render Applicant's method obvious.

Accordingly, it is respectfully requested that the rejection of claims 1-3 over Bryant be withdrawn.

In view of the foregoing comments, the Examiner is respectfully urged to reconsider and withdraw all rejections. It is believed this application is in condition for allowance. A Notice of Allowance is accordingly courteously solicited.

Respectfully submitted,

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